BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Appellant(s):	Dirk Beher, et al.
Application Number:	10/566,844
Filing Date:	February 1, 2006
Title of the Invention:	Treatment of Alzheimer's Disease and Related Conditions
Examiner:	Savitha M Rao
Art Unit:	1614

APPEAL BRIEF

STATEMENT OF THE REAL PARTY IN INTEREST

The real party in interest is Merck Sharp & Dohme Limited, a wholly owned subsidiary of Merck & Co., Inc.

STATEMENT OF RELATED CASES

None.

JURISDICTIONAL STATEMENT

The Board has jurisdiction under 35 U.S.C. 134(a). The examiner mailed a final rejection on April 29, 2009, setting a three-month shortened statutory period for response. The shortened statutory period for replying to the final rejection expired on July 29, 2009. A notice of appeal was filed on July 29, 2009. The time for filing an appeal brief is two months after the filing of a notice of appeal. Rule 41.37(c). The appeal brief is being filed on September 29, 2009.

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TABLE OF AUTHORITIES

STATUS OF AMENDMENTS

An Amendment after Final Rejection filed June 10, 2009, was entered by the examiner.

GROUNDS OF REJECTION TO BE REVIEWED

Rejection of Claim 7 as obvious over Ford-Hutchinson (EP 0 307 077) as evidenced by Patani (Patani et al., Chemical Reviews, 1996, vol. 96 (8), pages 3147-3176) in view of Watanbe (US 6,514,984).

STATEMENT OF FACTS

Fact 1. Ford-Hutchinson described a genus of tetrahydrocarbozole-1-alkanoic acids (page 4, lines 15 to page 5, line29 and claim 1). Fact 2. Ford-Hutchinson additionally discloses the compound 9-*p*-chlorobenzyl-6-isopropyl-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid (page 8, line 10-30, page 10, lines 1 and 11 and page 37, lines 25-40). Fact 3. Ford-Hutchinson describes the compounds therein as useful for improving cyclosporine therapy (page 2, line 4).

Fact 4. Patani describes the structure activity relationship of 1-[(2-hydroxyethoxy)methyl]-5-benzyluracils for inhibition of liver uridine phosphorylase (UrdPase) and demonstrates that substitution of CF_3 for Cl at the 3-

position resulted in less potent analogues (page 3172, column 1, first paragraph).

Fact 5. Patani describes the structure activity relationship of 3-(benzoylamino)benzodiazepines for antagonist activity at the chlolescystokinin-A (CCK-A) receptor and demonstrates that substitution of CF_3 for Cl at the 4-position of the benzoyl group resulted in retention of CCK-A activity (page 3172, column 1, second paragraph).

Fact 6. Watanbe describes a method for the prevention and treatment of Alzheimer's disease by administering to a human in need thereof an effective amount of a substituted tricyclic secretory phospholipase A2 ($sPLA_2$) inhibitor (abstract). Fact 7. Watanbe describes a genus of carbazole compounds. (col. 10, lines 11-65). Fact 8. Watanbe describes suitable formulations being those comprising a therapeutically effective amount of $sPLA_2$ inhibitor together with a pharmaceutically diluent or carrier, the composition being adapted for the particular route of administration. (col. 55, lines 49-57).

ARGUMENT

ERRORS IN REJECTION BASED ON FORD-HUTCHINSON AS EVIDENCED BY PATANI IN VIEW OF WATANBE

CLAIM 7

The examiner argues that one skilled in the medicinal chemistry art with knowledge of Ford-Hutchinson would have been motivated to modify compound

24 described therein to synthesize those presently claimed. Final Rejection mailed April 29, 2009, page 6, lines 1-8. In response, appellants previously pointed out to the examiner why the examiner is believed to have erred. Reply to Non-Final Office Action dated February 9, 2009, pages 1 to 3 and Amendment After Final Rejection dated June 10, 2009, page 4. The response is, first, the fact that a claimed subgenus is encompassed by a prior art genus is insufficient by itself to establish a *prima facie* case of obviousness. One skilled in the art must be motivated to select the claimed sub-genus from the disclosed prior art genus. Here, there are a number of possible substitutions taught by the genus of Ford-Hutchinson and there is no motivation for one skilled in the art to modify Ex. 24 of Ford-Hutchinson by substituting CF_3 at the 4-position of the benzyl portion of Formula III and a hydrocarbon of 2 to 10 carbon atoms on the benzylic carbon.

Second, none of the actual examples disclosed in Ford-Hutchinson have a hydrocarbon of 2 to 10 carbon atoms on the benzylic carbon, thus teaching away from the present invention. Appellants wish to point out an error in the arguments contained in the Reply to Non-Final Office Action dated February 9, 2009 at page 2, first paragraph. Compound 66 of Ford-Hutchinson contains a CF_3 group at the 4 position of the benzyl group.

Furthermore, appellants present a new argument that was not previously presented to the examiner. The new argument is that one skilled in the art would

not have selected Example 24 from Ford-Hutchinson as a lead compound from which to make further modifications to seek improved properties. Takeda Chemical Industries v. Mylan Laboratories, 492 F.3d 1350, 1357 (Fed.Cir.2007). In Ford-Hutchinson, test results are described for compounds 1, 37, 50 and 63, not 24.

The Examiner also argues that one of ordinary skill in the art would have been motivated to try out the range of substituents taught by Ford-Hutchinson to arrive at the instantly claimed compounds. Final Rejection mailed April 29, 2009, page 8, lines 8-10. The Examiner further argues that the instantly claimed compounds are explicitly suggested by Ford-Hutchinson within a finite list of compounds encompassed by the generic compounds and the exemplified compounds and as such renders the instantly claimed compounds and compositions obvious. Final Rejection mailed April 29, 2009, page 10, lines 13-16. In response, Appellants previously pointed out to the examiner why the examiner is believed to have erred. Reply to Non-Final Office Action dated February 9, 2009, page 3. The response is that obvious to try is not the proper standard to conduct an obviousness determination for chemical compounds. "In cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish a prima facie case of obviousness." Takeda, 492 F.3d at 1357.

The examiner further argues that Patani teaches that Cl and CF_3 are bioisosteres and one can be substituted for the other. Final Rejection mailed April 29, 2009, page 6, lines 9-11. In response, Appellants previously pointed out to the examiner why the examiner is believed to have erred. Reply to Non-Final Office Action dated February 9, 2009, pages 2 to 3. The response is that Patani teaches substitution on entirely different core molecules for different biologic targets and would in no way be utilized by the ordinarily skilled artisan in designing compounds that limit cyclosporine induced nephrotoxicity or modulate the action of gamma secretase. Furthermore, Patani itself demonstrates the unpredictability of the chemical arts as substitution of CF_3 for Cl resulted in less potent analogues for the demonstrated UrdPase inhibitors but retention of activity for the CCK-A receptor antagonists.

The Examiner further argues Watanbe provides additional motivation as structurally similar compounds and compositions have been shown to be used for the treatment of Alzheimer's disease. Final Rejection mailed April 29, 2009, page 8, lines 11-12. In response, Appellants previously pointed out to the examiner why the examiner is believed to have erred. Reply to Non-Final Office Action dated February 9, 2009, page 3. The response is that the instant claims require a $C(R^2)_2CO_2H$ group at a fixed position on the cyclohexene ring adjacent to the indole nitrogen. The nearest Watanbe comes to this is an amide or hydrazide

group, attached directly to the ring (no -C(R^2)- spacer) at the opposite end, i.e., pointing in entirely the wrong direction. Thus, Watanbe would in no way motivate the ordinarily skilled chemist to modify the compounds of Ford-Hutchinson to arrive at the compounds presently claimed.

Appellants wish to point out an error in the arguments contained in the Reply to Non-Final Office Action dated February 9, 2009 at page 3, second paragraph. The argument states that Watanbe does not specifically teach CF_3 substitution on the phenyl ring. However, Watanbe does not specifically teach 4-CF_3 substitution on the phenyl ring or substitution with 2 to 10 carbon atoms on the benzylic carbon.

Furthermore, appellants present a new argument that was not previously presented to the examiner. The new argument is that one skilled in the art would in no way combine the teachings of Ford-Hutchinson (improving cyclosporine therapy) with Watanbe (Alzheimer's disease) as the compounds disclosed therein are directed to unrelated utilities.

CONCLUSION

Appellants request that the Board of Patent Appeals and Interferences reverse the outstanding rejections of claim **7**.

Please charge deposit account 13-2755 for fees due in connection with this appeal brief. If any time extensions are needed for the timely filing of the present appeal brief, appellants petition for such extensions and authorize the charging of deposit account 13-2755 for the appropriate fees.

Respectfully submitted,

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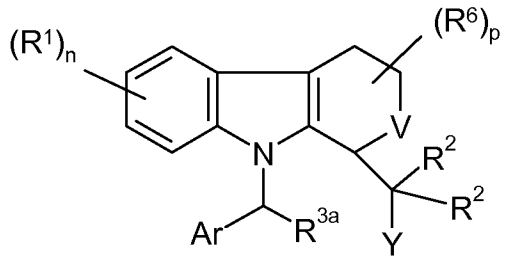
CLAIMS APPENDIX

Claim 7 (Rejected) A compound having formula III:



III

or a pharmaceutically acceptable salt thereof, wherein

V represents a bond, CH_2 or CH_2CH_2;

n is 0, 1, 2 or 3;

each R^1 is independently selected from nonaromatic hydrocarbon groups of up to 6 carbon atoms and $(CH_2)_q$-W where q is 0, 1 or 2 and W represents halogen, CN, CF_3, OR^4, $N(R^4)_2$, SR^4, CO_2R^4, tetrazole, $CON(R^4)_2$, $SO_2N(R^4)_2$, COR^5, $OCOR^5$ or phenyl or heteroaryl either of which optionally bears up to 3 substituents selected from halogen, CF_3, OCF_3, CN, OH, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio or C_{1-4}alkoxycarbonyl;

R^{3a} represents a hydrocarbon group containing from 2 to 10 carbon atoms which is optionally substituted with halogen, CF_3, C_{1-4}alkoxy or C_{1-4}alkylthio;

R^4 represents H or a hydrocarbon group of up to 7 carbon atoms, optionally substituted with halogen, CN, CF_3, OH, C_{1-4}alkoxy or C_{1-4}alkoxycarbonyl; or two R^4 groups attached to the same nitrogen atom may complete a 5- or 6-membered heterocyclic ring;

R^5 represents R^4 that is other than H;

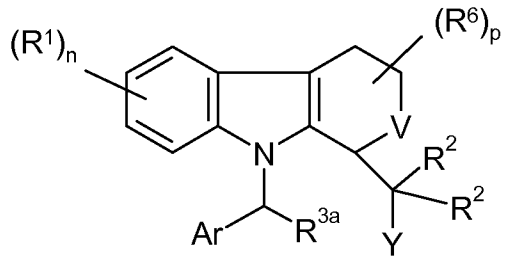
R^6 represents C_{1-6}alkyl, C_{2-6}alkenyl or phenyl, benzyl or heteroaryl, said phenyl, benzyl or heteroaryl optionally bearing up to 3 substituents selected from halogen, CN, CF_3, OCF_3, OR^4, CO_2R^4, COR^5, $OCOR^5$ and C_{1-4}alkyl;

p is 0, 1 or 2; and

Y represents CO_2H, Ar represents 4-trifluoromethylphenyl, and both R^2 groups represent H.

CLAIM SUPPORT AND DRAWING ANALYSIS APPENDIX

Claim 7 A compound having formula III:



{Page 14, line 25; original claim 7}

III

or a pharmaceutically acceptable salt thereof, **{Page 15, lines 3-4; original claim 7}**

wherein

V represents a bond, CH_2 or CH_2CH_2; **{Page 15, lines 1 to 2; Page 3, line 12; original claim 7}**

n is 0, 1, 2 or 3; **{Page 15, lines 1 to 2; Page 3, line 22; original claim 7}**

each R^1 is independently selected from nonaromatic hydrocarbon groups of up to 6 carbon atoms and $(CH_2)_q$-W where q is 0, 1 or 2 and W represents halogen, CN, CF_3, OR^4, $N(R^4)_2$, SR^4, CO_2R^4, tetrazole, $CON(R^4)_2$, $SO_2N(R^4)_2$, COR^5, $OCOR^5$ or phenyl or heteroaryl either of which optionally bears up to 3 substituents selected from halogen, CF_3, OCF_3, CN, OH, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-}

$_4$alkylthio or C_{1-4}alkoxycarbonyl; **{Page 15, lines 1 to 2; Page 3, line 23 to page 4, line 2; original claim 7}**

R^{3a} represents a hydrocarbon group containing from 2 to 10 carbon atoms which is optionally substituted with halogen, CF_3, C_{1-4}alkoxy or C_{1-4}alkylthio; **{Page 14, lines 27 to 28; original claim 7}**

R^4 represents H or a hydrocarbon group of up to 7 carbon atoms, optionally substituted with halogen, CN, CF_3, OH, C_{1-4}alkoxy or C_{1-4}alkoxycarbonyl; or two R^4 groups attached to the same nitrogen atom may complete a 5- or 6-membered heterocyclic ring; **{Page 4, line 6 to 9; original claim 7}**

R^5 represents R^4 that is other than H; **{page 4, line 10; original claim 7}**

R^6 represents C_{1-6}alkyl, C_{2-6}alkenyl or phenyl, benzyl or heteroaryl, said phenyl, benzyl or heteroaryl optionally bearing up to 3 substituents selected from halogen, CN, CF_3, OCF_3, OR^4, CO_2R^4, COR^5, $OCOR^5$ and C_{1-4}alkyl; **{ Page 15, lines 1 to 2; Page 4, lines 12-14; original claim 7}**

p is 0, 1 or 2; **{ Page 15, lines 1 to 2; Page 4, line 11; original claim 7}** and

Y represents CO_2H, Ar represents 4-trifluoromethylphenyl, and both R^2 groups represent H. **{Page 15, lines 8-10; original claim 7}**

MEANS OR STEP PLUS FUNCTION ANALYSIS APPENDIX

None.

EVIDENCE APPENDIX

None.

RELATED CASES APPENDIX

None.